Magnetic Resonance Imaging 63 (2019) 155–158

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Identification of carotid non-hemorrhagic lipid-rich necrotic core by magnetization-prepared rapid acquisition gradient-echo imaging: Validation by contrast-enhanced T1 weighted imaging

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1. Introduction

The rupture of carotid vulnerable atherosclerotic plaques is associated with ischemic cerebrovascular events [1,2]. Histologically, large non-hemorrhagic lipid-rich necrotic core (NH-LRNC) is one of the key characteristics of vulnerable plaques [3]. The presence of NH-LRNC in carotid arteries might speed the progression of atherosclerotic plaques [4] and the content of NH-LRNC is strongly related to the systemic cardiovascular outcomes [5]. In addition, NH-LRNC has been largely considered as a target of pharmaceutical treatment with statin. Therefore, it's important to identify the presence and area of NH-LRNCs in the clinical settings.

Multi-contrast magnetic resonance (MR) vessel wall imaging techniques have been widely utilized to detect and quantify NH-LRNCs in carotid arteries [6,7]. In particular, contrast-enhanced T1W (CE-T1W) imaging is considered as the reference of in vivo imaging technique for characterizing NH-LRNCs. CE-T1W imaging has been demonstrated to have good agreement with the histology in the measurements of mean percentage LRNC areas (LRNC area/wall area) [8]. However, the gadolinium-based contrast agent has the risk of developing nephrogenic systemic fibrosis [9]. CE-T1W imaging might not be applicable for patients with renal dysfunction and/or severe chronic kidney insufficiency. Therefore, a non-contrast enhanced MR imaging technique is warranted in the assessment of NH-LRNCs.

Several non-contrast enhanced MR imaging techniques have been proposed for evaluating NH-LRNCs. In previous studies, traditional T2W imaging has been proved to be able to identify NH-LRNCs. Because the performance of T2W was poorer than that of CE-T1W imaging in identifying NH-LRNCs [6,8], it is suggested to propose a non-contrast imaging approach that has a better performance than T2W imaging in identifying NH-LRNCs. It has been shown that high resolution 3D diffusion weighted imaging (DWI) is capable of detecting NH-LRNCs in vivo [10,11]. The apparent diffusion coefficient (ADC) values calculated from DWI could also be used to identify NH-LRNCs [12]. However, the clinical application of DWI is still hampered by bulk physiological motion and magnetic susceptibility. Recently, a new technique of multi-contrast atherosclerosis characterization (MATCH) has been developed to identify carotid plaque components including NH-LRNCs [13,14]. The MATCH provides three different contrast weightings including hyper-T1W, T2W and gray blood with a single 5-min scan. Nevertheless, the MATCH sequence is more sensitive to the motion compared with the traditional multi-contrast imaging techniques [13]. Most recently, 3D magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) imaging, a traditional heavily T1W imaging, has been demonstrated to have the potential in identification of carotid NH-LRNCs [15]. This study aims to determine the capability of 3D MP-RAGE imaging in evaluating carotid artery NH-LRNCs compared with T2W validated by CE-T1W imaging.

2. Materials and methods

2.1. Study sample

Asymptomatic subjects with carotid atherosclerotic plaques on ultrasound were recruited in this study. All recruited subjects underwent carotid multicontrast MR vessel wall imaging for both carotid arteries. Clinical information including age, gender, blood pressure, level of lipoproteins and history of smoke was collected. The study protocol was reviewed and approved by the local Institution Review Board prior to the initiation of this study and the written consent was obtained from each subject.

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https://doi.org/10.1016/j.mri.2019.08.023
Received 22 March 2019; Received in revised form 8 May 2019; Accepted 15 August 2019

2.2. Carotid MR imaging

Carotid MRI was performed on a 3.0T MR scanner (*Achieva TX, Philips Healthcare, The Netherlands*) with a dedicated 8-channel carotid coil (*Shanghai Chenguang Medical Technologies Co., LTD, Shanghai, China*) at Center for Biomedical Imaging Research in Tsinghua University. The time of flight (TOF), pre- and post-contrast T1W, T2W, and MP-RAGE imaging sequences were performed: TOF: turbo field echo (TFE); repetition time (TR)/echo time (TE) 20/5 ms; flip angle 20°; pre- and post-contrast T1W: turbo spin echo (TSE); TR/TE 800/10 ms; flip angle 90°; T2W: TSE; TR/TE 4800/50 ms; flip angle 90°; and MP-RAGE: TFE; TR/TE 9/5.5 ms; flip angle 15°. The in-plane FOV and spatial resolution was 140 × 140 mm^2 and 0.6 × 0.6 mm^2 for all sequences. The CE-T1W imaging was performed immediately after the injection of gadolinium-based agent (*Magnevist, Bayer Schering Pharma, Germany*) with 0.1 mmol/kg. The MR imaging was centered to the bifurcation of carotid arteries with larger plaque bilaterally.

2.3. Image analysis

All MR images were interpreted by two reviewers with > 5 years' experience in neurovascular MRI. The MR image quality was assessed with 4-point scale: 1 = poor; 2 = adequate; 3 = good; and 4 = excellent [16]. Slices with image quality < 2 or intraplaque hemorrhage were excluded. The included images were divided into the following three different MR sequence combinations: 1) TOF, T1W, and T2W; 2) TOF, T1W, and MP-RAGE; and 3) TOF, T1W, and CE-T1W. The contours for lumen and outer wall at each axial location were outlined on the TOF and T1W images and mapped to T2W, MP-RAGE and CE-T1W images. The presence or absence and the area of carotid NH-LRNCs were evaluated by two reviewers with an interval of one month to minimize the bias of memory and consensus. NH-LRNC was defined as components with iso-intense on TOF and T1W images and hypointense on T2W, MP-RAGE (66% signal drop compared with muscle [15]) and CE-T1W images using published criteria [8]. CE-T1W images were considered as reference in identifying NH-LRNCs because of its strong correlation with histology [8]. All the MR image analyses were performed manually using custom designed software "CASCADE" (*University of Washington, Seattle, USA*) [17].

2.4. Statistical analysis

Continuous variables were described as mean and standard deviation and categorical variables were presented with percentage. The agreement of MP-RAGE or T2W imaging with CE-T1W imaging in identification of NH-LRNCs was evaluated using Cohen's kappa analysis. Repeated-measures analysis of variance with mixed procedure and Bonferroni adjustment for post hoc comparisons was used to compare the capability of MP-RAGE and T2 imaging in identifying NH-LRNCs with CE-T1W imaging as reference. A p value < 0.017 (0.05 divide by the times of comparisons) was considered statistically significant. The area-under-the-curve (AUC) from receiver operating characteristics analysis of MP-RAGE or T2W imaging in identifying the presence of NH-LRNC was calculated with CE-T1W imaging as reference.

The area of NH-LRNCs was compared between MP-RAGE and CE-T1W imaging and between T2W and CE-T1W imaging using paired t-test when NH-LRNCs were detected by these sequences. The intraclass correlation coefficient (ICC) and Bland-Altman were utilized to assess the agreement between MP-RAGE and CE-T1W imaging and between T2W and CE-T1W imaging in measuring NH-LRNCs when present. A p value < 0.05 was considered as statistically significant.

All statistical analyses were performed using SPSS 16.0 (*SPSS Inc., Chicago, IL*) and SAS (*SAS Inc., North Carolina, NC*).

Table 1
Clinical information and carotid plaque features of subjects (N = 51).

	No. (%) or mean ± SD
Clinical information	
Age, years	60.7 ± 9.9
Gender, male	39 (76.5)
History of smoking	34 (66.7)
Systolic blood pressure, mm Hg	144.3 ± 24.2
Diastolic blood pressure, mm Hg	88.0 ± 14.8
LDL, mmol/L	2.6 ± 0.9
HDL, mmol/L	1.0 ± 0.3
TC, mmol/L	4.2 ± 1.0
TG, mmol/L	1.7 ± 0.9
Plaque features	
Mean lumen area, mm^2	39.6 ± 22.0
Mean wall area, mm^2	24.6 ± 11.1
Mean total vessel area, mm^2	64.2 ± 31.3
Maximum wall thickness, mm	1.3 ± 0.7
Mean normalized wall index, %	39.7 ± 6.9

3. Results

Of the 53 recruited patients, 2 were excluded due to poor image quality. Of the remaining 51 subjects (mean age, 60.7 ± 9.9 years; 39 males), 1894 slices from 101 arteries (one artery was excluded due to poor image quality) were included in this study. The clinical information and plaque features of 51 subjects were detailed in Table 1.

3.1. Qualitative identification of NH-LRNCs

All 51 subjects were found to have NH-LRNCs on MP-RAGE, T2W and CE-T1W images. Of 101 arteries from 51 subjects, 98 (97.0%), 96 (95.0%) and 97 (96.0%) were found to have NH-LRNCs on MP-RAGE, T2W and CE-T1W images, respectively. Of 1894 slices from 101 arteries, 582 (30.7%), 448 (23.7%), 551 (29.1%) slices were found to have NH-LRNCs on MP-RAGE, T2W and CE-T1W images, respectively. Moderate agreement was found between MP-RAGE and CE-T1W imaging (kappa = 0.52) and between T2W and CE-T1W imaging (kappa = 0.59) in identification of NH-LRNCs (Table 2). After adjust for the relevance of slices and sides, the MP-RAGE and T2W imaging both appeared significant difference in identification of NH-LRNCs compared with CE-T1W imaging ($p < 0.001$). The sensitivity of NH-LRNCs on MP-RAGE images was significantly higher than that on T2W images (68.2% vs. 63.0%, $p < 0.001$). The positive predictive value of NH-LRNCs on MP-RAGE images was lower than that on T2W images (64.6% vs. 77.5%, $p < 0.001$). The AUC of MP-RAGE and T2W imaging was 0.77 and 0.78 in identifying the presence of NH-LRNC with CE-T1W imaging as reference, respectively.

3.2. Quantitative identification of NH-LRNCs

For NH-LRNCs detected by both MP-RAGE and CE-T1W imaging, no significant difference was found in the area of NH-LRNCs between MP-RAGE and CE-T1W imaging (6.1 ± 6.1 mm^2 vs. 6.0 ± 6.6 mm^2,

Table 2
The agreement between MP-RAGE and CE-T1W imaging and between T2W and CE-T1W imaging in the identification of NH-LRNCs.

		CET1		Total
		Absence	Presence	
MP-RAGE	Absence	1137	175	1312
	Presence	206	376	582
T2	Absence	1242	204	1446
	Presence	101	347	448
Total		1343	551	1894

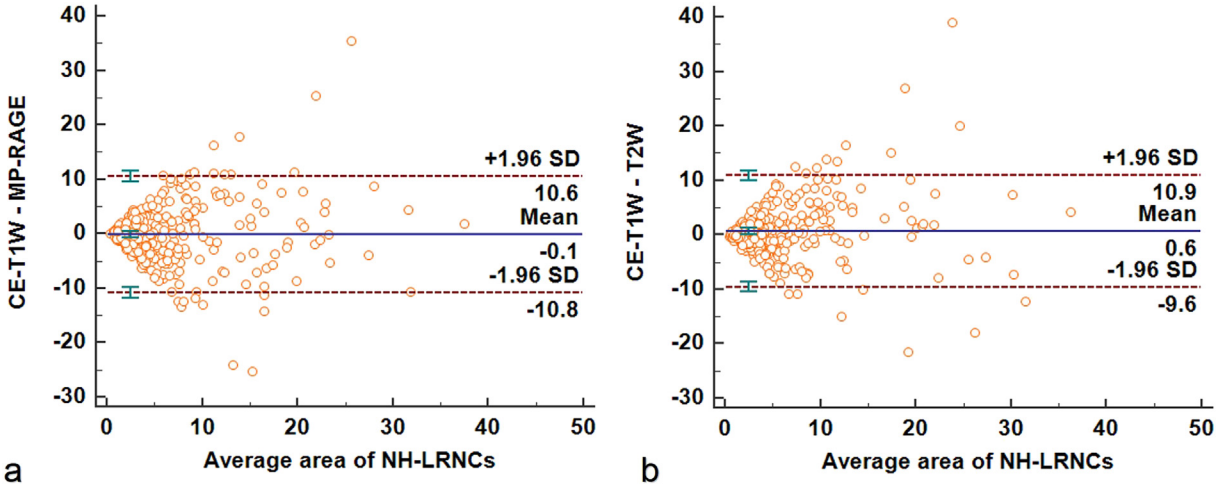

Fig. 1. Bland-Altman analysis of MP-RAGE (a)/T2W (b) imaging and CE-T1W imaging in identifying NH-LRNCs.

p = 0.628). In contrast, the area of NH-LRNCs measured by T2W imaging was significantly smaller than that measured by CE-T1W imaging ($5.5 \pm 5.9\,mm^2$ vs. $6.1 \pm 6.6\,mm^2$, p = 0.023). Good agreement can be observed in quantification of NH-LRNCs between MP-RAGE and CE-T1W imaging (ICC = 0.774, 95% CI 0.723–0.815) and between T2W and CE-T1W imaging (ICC = 0.791, 95% CI 0.742–0.831). Bland-Altman analysis revealed that the bias of area of NH-LRNCs measured by MP-RAGE was smaller than that measured by T2W ($-0.1 \pm 5.5\,mm^2$ vs. $0.6 \pm 5.3\,mm^2$) compared with CE-T1W imaging (Fig. 1).

An example that MP-RAGE successfully identified carotid NH-LRNCs is shown in Fig. 2. NH-LRNCs were identified and quantified on three different MR sequence combinations: 1) TOF, T1W and MP-RAGE (a–c); 2) TOF, T1W and T2W (a, b, d); 3) TOF, T1W and CE-T1W (a, b, e) images. The area of NH-LRNCs was 8.2 mm^2, 4.0 mm^2, 10.1 mm^2 on MP-RAGE (h), T2W (i) and CE-T1W (j) images, respectively.

4. Discussion

This study determined the capability of MP-RAGE imaging in identification of NH-LRNCs compared with T2W imaging validated by CE-T1W imaging. Moderate to good agreements were found in identification and quantification of NH-LRNCs between MP-RAGE and CE-T1W imaging. MP-RAGE detected more NH-LRNCs compared with T2W, suggesting that MP-RAGE might be a more sensitive non-contrast enhanced imaging technique for lipid-rich atherosclerotic plaques. Furthermore, MP-RAGE imaging was comparable with CE-T1W imaging in quantifying NH-LRNCs and had smaller bias in measuring the area of NH-LRNCs compared to T2W imaging. Our findings suggest that MP-RAGE imaging might be a better non-contrast enhancement technique than T2W imaging in identification and quantification of NH-LRNCs.

In this study, moderate agreement was found in the identification of NH-LRNCs between MP-RAGE or T2W imaging and CE-T1W imaging. Because LRNCs without IPH have shorter T2 values (< 42 ms) [18] than fibrous tissue of the arterial wall, T2W imaging can be a potential technique to identify NH-LRNCs. Previous study proved that T2W imaging showed moderate to strong agreement with histology in identification of NH-LRNCs [6,19]. In contrast, the T1 value of LRNCs and fibrous tissues in the vessel wall was 519 ms and 596 ms, respectively [20]. Therefore, it is challenging to distinguish NH-LRNCs from fibrous tissues using traditional T1W imaging. Beneficial from the use of

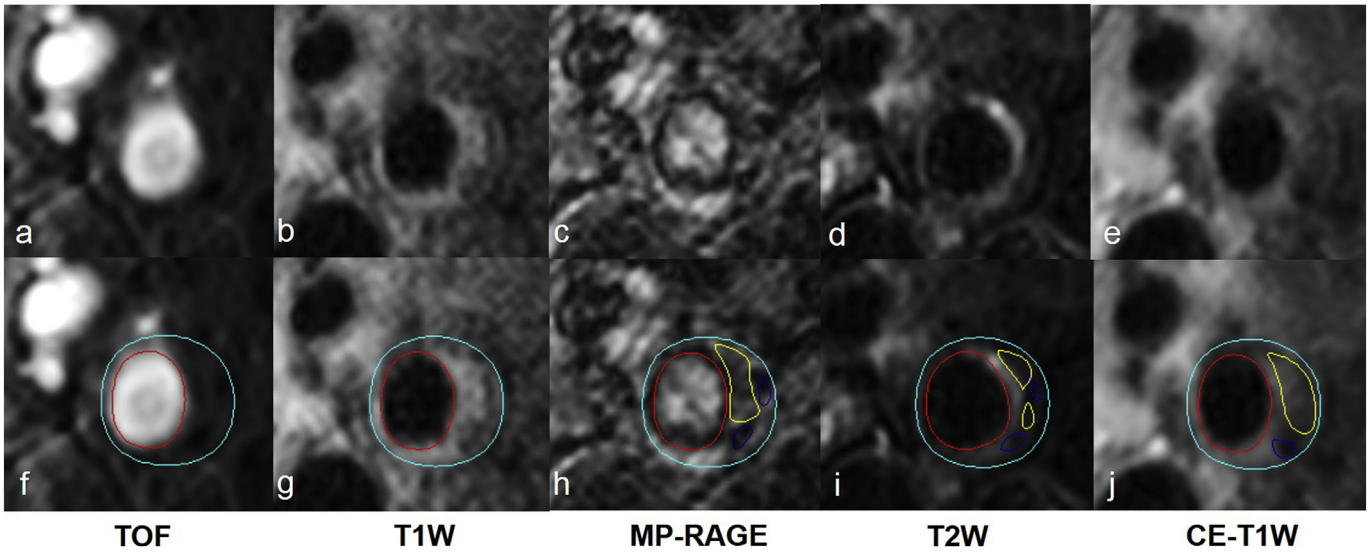

Fig. 2. NH-LRNCs (yellow) were identified and quantified on three different MR sequence combinations. The original images were shown in a–e. The boundaries of lumen and wall were outlined on TOF and T1W images (f, g). The area of NH-LRNCs was 8.2 mm^2, 4.0 mm^2, 10.1 mm^2 on MP-RAGE (h), T2W (i) and CE-T1W (j) images, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

gadolinium-based contrast agent, CE-T1W imaging had better performance than T2W imaging in identification and quantification of NH-LRNCs validated by histology [8], owing to the increased signal contrast between enhanced fibrous tissues and non-enhanced NH-LRNCs [21]. Theoretically, MP-RAGE can also provide a better contrast between NH-LRNCs and fibrous tissues than traditional T1W images because the magnetization in MP-RAGE imaging needs more time to recover than traditional T1W imaging [15]. Our study further compelled the evidence that, as non-contrast enhanced imaging techniques, both T2W and MP-RAGE sequences are capable of identifying NH-LRNCs.

The present study showed that MP-RAGE imaging could identify more NH-LRNCs compared to T2W imaging, suggesting it might be more sensitive to the NH-LRNCs. We also found that, in the quantitative measurements of NH-LRNCs, MP-RAGE imaging had a better performance than T2W imaging. Previous study also showed that MP-RAGE imaging had greater AUC than T2W imaging in identifying NH-LRNCs [15]. NH-LRNCs contain complex components including cholesterol crystal, debris of apoptotic cells, particles of calcium, etc. The signal intensity of NH-LRNCs on T2W imaging appeared a wide range from isointense to hypointense. The lesions with intraplaque hemorrhage were excluded in this study because LRNCs with intraplaque hemorrhage may appear hypointense, isointense or hyperintense on T2W images which cannot be easily distinguished from those without intraplaque hemorrhage by T2W imaging [16]. In addition, T2W imaging is more sensitive to the tissues with inflammatory cells infiltrated [22]. The hyperintensity of loose matrix and inflammation on T2W images might disturb the identification of the boundary of NH-LRNCs. On MP-RAGE imaging, NH-LRNCs appeared uniform hypointense. The present study showed that MP-RAGE imaging was comparable with T2W imaging in qualitatively identifying NH-LRNCs and better than T2W imaging in quantitatively measure the area of NH-LRNCs. Accurate quantification of LRNCs is important because the area of LRNCs has been demonstrated to be strongly associated with the occurrences and outcomes of cardiovascular events [2,5]. Our findings suggested that MP-RAGE imaging might be a better non-contrast enhanced MR imaging technique in identification of NH-LRNCs than T2W imaging.

There are several limitations in this study. First, CE-T1W imaging was considered as reference in identification of NH-LRNCs in the present study. Future studies with histological validation are warranted. Second, fibrous caps covering LRNCs on all three MR imaging sequences were not evaluated in this study. Due to the limited signal-to-noise ratio (SNR) and spatial resolution, it is challenging to distinguish thin fibrous caps from LRNCs. A higher spatial resolution and SNR MR imaging technique is needed to identify fibrous caps in future. Third, the SNR and contrast-to-contrast ratio (CNR) of MP-RAGE are lower than those of CE-T1W imaging. To improve the SNR and CNR of MP-RAGE imaging sequence, particularly for delineating the boundaries of arterial lumen and wall, is suggested in the future work.

5. Conclusions

In conclusion, MP-RAGE sequence might be a better non-contrast enhanced imaging technique than T2W imaging for assessing non-hemorrhagic lipid-rich necrotic cores in carotid arteries.

Declaration of competing interest

None.

Acknowledgements and disclaimer

This work was supported by grants of Beijing Municipal Science and Technology Commission (D171100003017003) and National Natural Science Foundation of China (81271536; 81361120402). The study protocol was approved by the local Institution Review Board. Information presented are based on research and are not commercially available.

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